

REMARKS

Status of the claims

Upon entry of these remarks, claims 89-95, 98-104, 107-110, 113-116, 119, 121, 126-130, 133, 135, 140-144, 147, 149, 212-218, 221-227, 230-233, 236-242, 245-256, 259-267, and 270-278 will be pending in this application. Claims 1, 17, 19, 26-88, 96, 97, 105, 106, 111, 112, 117, 118, 120, 122-125, 131, 132, 134, 136-139, 145, 146, 148, 150-211, 219-220, 228, 229, 234, 235, 243, 244, 257, 258, 268, and 269 have been canceled without prejudice or disclaimer. Applicants' purpose in canceling these claims is solely to simplify, and therefore facilitate, prosecution of the instant application. Applicants assert that each of the canceled claims is fully enabled and satisfies the statutory requirements under 35 U.S.C. § 112. Applicants reserve the right to pursue the subject matter of the claims cancelled herein in one or more continuing applications.

Support for the newly added and amended claims is found throughout the specification as filed, and no new matter has been introduced.

Claims 113, 126, and 140 have been amended to recite a method of treating "an immunodeficiency." As indicated in Applicants' Provisional Election of August 20, 2001, support for claims directed to using Neutrokin- α polypeptides to treat immunodeficiencies may be found, for example, on pages 18-20 and 322-324 as well as on pages 291-295 and 326-327 of the specification as filed. Support for new (claims 275-278) or amended claims (claims 119, 121, 133, 135, 147 and 149) directed to using Neutrokin- α polypeptides to treat common variable immunodeficiency (CVID) or Selective IgA deficiency may be found, for example, on pages 292-295, the fifth paragraph on page 325, the fifth and seventh paragraphs on page 326, and the paragraph spanning pages 327-328 of the specification as filed.

Claims 89, 98, 126, 140, 212, 221, 230, 236, and 250 have been amended to recite that the claimed Neutrokin- α polypeptide "modulates lymphocyte proliferation, *differentiation or survival*" (amendment indicated in italics). Support for these amendments may be found, for example, in the specification as filed at the third full paragraph on page 18, the paragraph spanning pages 46-47, the second paragraph on page 56, and the paragraph spanning pages 81-82, and Examples 6 and 7.

Additionally, claims 89, 98, 212, 221, 236, and 250 have been amended to make the formatting of the claims more consistent. The subparts of claim 98 have been properly

identified as (a)-(c) rather than (d)-(f). The dependencies of claims 142, 144, 147, 149, 226, and 233 have also been corrected.

Thus, no new matter has been added by way of amendment.

For the Examiner's convenience, a Clean Version of the Entire Set of Pending Claims (including amendments made herein) as allowed for under 37 C.F.R. §1.121(c)(3) is enclosed.

Substitute Specification

In accordance with the Examiner's request that Applicants check the specification for minor errors, Applicants provide herewith a substitute specification as well as a Version of the Substitute Specification with Markings to Show Changes Made.

The undersigned attorney of record hereby states under 37 C.F.R. §1.125(b)(1) that the substitute specification filed herewith contains no new matter. Each of the amendments to the specification are shown in boldfaced text in the Version of the Specification With Markings to Show Changes Made submitted herewith in which insertions are indicated by underlining and deletions are indicated by strikeout. The amendments either (1) correct grammatical and/or clerical errors (2) amend the specification to add SEQ ID NOs for sequences disclosed in the specification as filed, or (3) were made and entered previously (i.e., the amendments proposed in the Preliminary Amendment filed July 28, 2000 have been entered into the Substitute Specification).

Title

The Examiner objected to the title of the application alleging that it was not descriptive of the claimed invention. In accordance with the Examiner's suggestion, Applicants have amended the title to "Methods of Treatment of Immune System Related Disorders Using Neutrokine-alpha." This amendment has been incorporated into the Substitute Specification submitted herewith.

Replacement Sequence Listing

The Substitute Sequence Listing submitted herewith has been amended to bring the Sequence Listing into compliance with the 37 C.F.R. §1.821- §1.825. Briefly, the amendments to the Sequence Listing include: (a) amendment of the header information to

correctly identify the present application and the applications to which it claims priority; (b) amendment of the header information preceding primer sequences (SEQ ID NOS: 10-17, 24-26, 31-36 and 39-42) to bring them into the appropriate format; (c) amendments to SEQ ID NO:38 to make the Sequence Listing correctly reflect SEQ ID NO:38 as defined in the specification, for example at pages 129-130; and (d) to add SEQ ID NOS:39-42 which correspond to sequences disclosed in the specification at page 420, lines 2-3 and page 421, lines 15-16). Each of the amendments is supported by the specification as originally filed and no new matter has been introduced.

Rejections under 35 U.S.C. §112, first paragraph

Claims 26-274 are rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement and written description.

A. Enablement Rejection

The Examiner rejected claims 26-164 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement stating that:

[T]he specification, while being enabling for a method of stimulation of B-lymphocyte proliferation comprising administering to an individual, an effective amount of a full length protein consisting of an amino acid sequence of SEQ ID No.2, but does not reasonably provide enablement for a method of treating ‘an immune system disease or disorder’ or ‘an autoimmune disease or disorder’ or ‘immunodeficiency’ or for stimulating B-lymphocyte proliferation, comprising administering to an individual a therapeutically effective amount of ‘any’ fragments, derivatives, fusion peptides, or variants, or fusion peptides of variants of SEQ ID No.2. (*See*, Paper No. 8, Paragraph spanning pages 3-4.)

The Examiner continues on page 4 of Paper No. 8:

There are two different issues of scope of enablement in this rejection:

- (a) stimulation of B-lymphocyte proliferation with full length polypeptide of SEQ ID No.2, and/or all of the contemplated fragments, fusion peptides and derivatives of SEQ ID No.2; and
- (b) treatment of all immune system diseases or disorders, autoimmune diseases or disorders, or immunodeficiencies by administering full length polypeptide of SEQ ID No.2, and/or all of the contemplated fragments, fusion peptides and derivatives of SEQ ID No.2.

Preliminarily, Applicants bring to the Examiner's attention that Applicants have cancelled:

- claims 26-61 and 154-211 drawn to methods of treating an immune system disease or disorder; and
- claims 62-88 drawn to methods of treating an autoimmune disease or disorder.

Additionally, Applicants have amended claims 113, 126, and 140 to recite a method of treating "an immunodeficiency." Applicants' purpose in canceling or amending these claims is solely to simplify, and therefore facilitate, prosecution of the instant application. Applicants assert that each of the cancelled claims is fully enabled and satisfies the statutory requirements under 35 U.S.C. § 112. Applicants reserve the right to pursue the subject matter of the claims cancelled herein in one or more continuing applications.

As Applicants have cancelled the above claims, Applicants will only rebut the present rejection insofar as it applies to the pending claims.

Neutrokin-alpha polypeptides may be used to treat immunodeficiencies.

The Examiner acknowledges that the specification is "enabling for a method of stimulation of B-lymphocyte proliferation comprising administering to an individual, an effective amount of a full length protein consisting of an amino acid sequence of SEQ ID No.2." (*See*, Paper No. 8, bottom of page 3), but contends that "it is not feasible for one of skill in the art to treat unnamed ...immunodeficiency as recited in the instant claims." (Paper No. 8, page 9, lines 8-9).

Applicants acknowledge the Examiner's statement that the specification is enabling for a method of using full-length Neutrokin-alpha polypeptide to stimulate lymphocyte

proliferation but respectfully disagree that one of skill in the relevant arts is not enabled by the specification to use Neutrokin- α polypeptides to treat immunodeficiencies.

The M.P.E.P. states in § 2164.08:

The Federal Circuit has repeatedly held that “the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without ‘undue experimentation’.” *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art.

Applicants assert that the specification provides all that is necessary to enable one of skill in the art to practice the claimed methods. First and foremost, the specification discloses that Neutrokin- α polypeptides are useful to treat immunodeficiencies, to stimulate leukocyte proliferation, differentiation or survival, and to enhance host defenses against infection. (See, for example page 18, third full paragraph, the paragraph spanning pages 46-47, the second paragraph on page 56, and pages 81-83, pages 320-324, page 344 of the specification as filed.) This disclosure is present in the earliest patent application to which the present application claims priority, namely international patent application PCT/US96/17957. These activities of Neutrokin- α have been corroborated by Applicants own later filed applications as well as in numerous publications by Applicants and others. (Please refer to the many post filing date references submitted with the Revised form PTO-SB-08 on August 20, 2001 such as Khare et al. (A55), McKay et al. (A57), and Schneider et al (A62). As disclosed in the specification (see, for example, Example 6), the soluble form of Neutrokin- α (corresponding to amino acids 134-285 of SEQ ID NO:2) is able to induce B cell proliferation in *in vitro* costimulation assays as well as to increase serum immunoglobulin levels in _____ Neutrokin- α treated mice. Neutrokin- α has also been shown to enhance humoral immune responses and function as a B cell survival factor (See, e.g., Do et al., cited as reference A50 submitted August 20, 2001). These observations of Neutrokin- α s biological activity would lead one of skill in the art to the conclusion that Neutrokin- α would be useful for treating immunodeficiencies and for stimulating immune function.

Assays to test a polypeptide’s ability to modulate lymphocyte proliferation, differentiation and/or survival are, and were at the earliest priority date of the present application, routine for one of skill in the art to perform. Thus, it would be routine for one of

skill in the art to determine if a Neutrokin- α polypeptide fragment or variant can modulate lymphocyte proliferation, differentiation and/or survival and therefore would be useful to stimulate leukocyte proliferation, differentiation or survival, to enhance host defenses against infection, or to treat an immunodeficiency.

The application further gives guidance as to how one of skill in the art can formulate and administer Neutrokin- α polypeptides to a patient. (see, e.g., pages 347-355 of the specification as filed). Applicants submit that the one skilled in the relevant arts, enlightened by the teaching of the present specification and armed with the knowledge available in the art at the time of filing of the earliest priority document of the captioned application, would be more than capable of using Neutrokin- α polypeptide to treat immunodeficiencies.

The Examiner also finds the specification lacking in enablement because there is allegedly no guidance as to the selection of patient population or to what are the symptoms that should be alleviated. Applicants respectfully disagree with this basis for the rejection.

Applicants submit that such information regarding the selection of a patient population for the treatment of immunodeficiencies and determining the alleviation of symptoms is well within the abilities of one skilled in the relevant arts. For example, common variable immunodeficiency (CVID) is defined by The Merck Manual¹, as a “heterogeneous disorder occurring equally in both sexes and characterized by the onset of recurrent bacterial infections, usually in the 2nd or 3rd decade of life as a result of markedly decreased Ig [immunoglobulin] and antibody levels.” In general, a normal individual has a serum IgG levels in the range of 560-1800 mg/dL. CVID patients have low serum IgG levels (≤ 400 mg/dL). Just as one of skill in the art is able to diagnose a patient with an immunodeficiency, one of skill in the art can also determine if symptoms are being alleviated by treatment, for example as measured by increased serum IgG levels. Similarly, patients with Selective IgA deficiency have < 5 mg/dL of serum IgA with normal levels of other immunoglobulins and intact cellular immunity; accordingly, effective treatment of this disorder would result in increased serum IgA levels.

Thus, it is clearly within the abilities of one of skill in the relevant arts to identify a population of patients suffering from an immunodeficiency and to determine if treatment with Neutrokin- α alleviates their symptoms without undue experimentation.

¹ The Merck Manual of Diagnosis and Therapy, 16th ed. Edited by Robert Berkow et al. Merck Research Laboratories, Rahway, N.J. 1992, page 313.

Accordingly, Applicants respectfully request that this aspect of the rejection (subpart (a) quoted above) under 35 U.S.C. § 112, first paragraph, be withdrawn.

The Polypeptides Used in the Claimed Methods are Fully Enabled

The Examiner contends that:

No guidance is provided to enable one of skill in the art to test each of these numerous variants of the instant SEQ ID No.2 to achieve therapeutic benefit in various unnamed immune system related disorders. The disclosure fails to provide any details of having used the polypeptides generated with N- terminal and C-terminal deletion mutants or fusion peptides. Particularly, the sequence 134-285 of SEQ ID No.2, much emphasized in the claims as being equivalent to full length polypeptide of SEQ ID No.2, has not been disclosed to have been used for any of the examples....It is not feasible for one of skill in the art to treat an individual with unnamed immune system related diseases or disorder with any of the several contemplated fragments covering different portions of SEQ ID No.2. (Paper No. 8, pages 9-10).

Applicants disagree with this basis for the rejection under 35 U.S.C. § 112, first paragraph.

Preliminarily, Applicants note that the Examiner is mistaken concerning the absence of an Example using the Neutrokin- α polypeptide corresponding to amino acid residues 134-285 of SEQ ID NO:2. The data in Example 6 was generated using the soluble form of the Neutrokin- α protein which corresponds to amino acids 134 to 285 of the full length protein. See, for example, the specification at the bottom of page 412 and the section entitled "Purification of Recombinant Neutrokin- α " on page 420.

Applicants also remind the Examiner that the enablement requirement of 35 U.S.C. § 112, first paragraph requires nothing more than objective enablement. A specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of § 112, unless there is reason to doubt the objective truth or accuracy of the statements relied upon therein for enabling support. *Staehelin v Secher*, 24 USPQ2d 1513, 1516 (B.P.A.I. 1992), *In re Marzocchi*, 169 USPQ 367 (C.C.P.A. 1971); *In re Brana* 34 USPQ2d 1437, 1441 (Fed. Cir. 1995).

As Judge Rich explained in *In re Vaeck*, 20 USPQ2d 1438, 1445 (Fed.Cir. 1991), the statutory enablement requirement is satisfied if the specification "adequately guides the worker to *determine*, without undue experimentation, which species among all those

encompassed by the claimed genus possess the disclosed utility" (emphasis provided). Since the disclosed or otherwise known methods of making and screening polypeptides (and fragments or variants thereof) may be used to make and then *determine*, without undue experimentation, whether a given polypeptide encompassed by the claims is able to modulate lymphocyte proliferation, differentiation or survival and to determine if those polypeptides will be useful in the treatment of immunodeficiencies, the enablement requirement is fully satisfied. *In re Wands*, 8 USPQ2d at 1404; *Ex parte Mark*, 12 USPQ2d 1904, 1906-1907 (B.P.A.I. 1989).

Applicants submit that the specification provides ample guidance for one of ordinary skill in the art to routinely make the polypeptides described in the claims and to use them in the claimed methods. For example, the specification discloses both the nucleic acid and amino acid sequences of Neutrokin- α , routine cloning methods, Neutrokin- α activity, and biological assays including, for example, assays to determine if a polypeptide modulates lymphocyte proliferation, differentiation or survival. The specification also describes that Neutrokin- α polypeptides (and fragments and derivatives thereof) may be used to treat immunodeficiencies. (*See, e.g.*, the specification at pages 85-99 and Examples 1-3, page 18, third full paragraph, pages 81-82, pages 291-295, in the paragraph spanning pages 300-301, the second full paragraph on page 302, pages 322-324, pages 326-7, Examples 6 & 7 and pages 347-355; please also refer to Sambrook et al. cited on page 384, lines 10-13).

Moreover, the skill in the art of molecular biology is high. The skilled molecular biologist, enlightened by the teaching of the present specification and armed with the knowledge available in the art at the time of filing of the earliest priority document of the present application, would be more than capable of routinely making proteins with at least 90% or 95% sequence identity with the amino acid sequence of SEQ ID NO:2 or a fragment thereof (e.g. amino acids 134-285 of SEQ ID NO:2) that display Neutrokin- α activity as encompassed by the claims. In addition, the instant specification explicitly teaches for example, assays which could be used to measure the ability of a polypeptide to modulate lymphocyte proliferation, differentiation or survival. Thus, the skilled artisan could readily and routinely test whether a protein with at least 90% or 95% sequence identity with the amino acid sequence of SEQ ID NO:2 or a fragment thereof (e.g. amino acids 134-285 of SEQ ID NO:2) has such activity and is useful in the claimed methods of treatment.

In view of the foregoing, Applicants respectfully request that this aspect of the rejection (subpart (b) in the passage quoted above) under 35 U.S.C. §112, first paragraph, be withdrawn.

A. Written Description Rejection

The Examiner rejected claims 26-274 for allegedly “containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.” (See, paper No. 8, page 11).

The test for written description is whether one skilled in the art could reasonably conclude that the inventor has possession of the claimed invention in the specification as filed *Vas Cath v. Mahurkar*, 935 F.2d 1555, 1563 19 U.S.P.Q. 2d 1111, 1116 (Fed. Cir. 1991); M.P.E.P. § 2163.02. The Federal Circuit recently re-emphasized the well settled principle of law that, “[t]he written description requirement does not require the Applicant to describe exactly the subject matter as claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [they] invented what is claimed” *Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989, 54 U.S.P.Q.2d 1227 (Fed. Cir. 2000).

As argued above in the section regarding enablement of the claimed invention, making and characterizing Neutrokin- α polypeptides would have been routine for one of skill in the art, as would have been the methods of using these polypeptides to treat an immunodeficiency at the time of the filing of this application and of the earliest application to which this application claims priority.

Moreover, Applicants have provided the polypeptide and nucleotide sequences of Neutrokin- α and disclosed that Neutrokin α can modulate lymphocyte proliferation, differentiation, and survival. The specification also describes that Neutrokin- α polypeptides (and fragments and derivatives thereof) may be used to treat immunodeficiencies. Applicants have also provided guidance as to routes of administration and dosaging. (See, e.g., the specification at the third full paragraph on page 18, pages 81-82, pages 291-295, in the paragraph spanning pages 300-301, the second full paragraph on page 302, pages 322-324, pages 326-7, Examples 6 & 7 and pages 347-355). To use Judge Rich’s now famous metaphor, Applicants specification has “blazed a trail through the forest,” (*In re Ruschig*, 379 F.2d 990, 994-5, 154 U.S.P.Q. 118), guiding those skilled in the art to the claimed invention.

For all of the above reasons, Applicants submit that one skilled in the art would reasonably conclude that Applicants had possession of the Neutrokin- α polypeptides and the claimed methods on the effective filing date of the present application. Accordingly, Applicants respectfully request that the written description rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

CONCLUSION

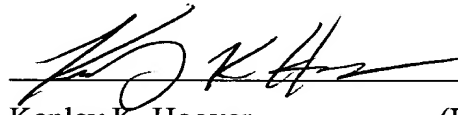
Applicants respectfully request that the amendments and remarks of the present Amendment be entered and made of record in the present application.

In view of the foregoing remarks, applicants believe that this application is now in condition for allowance. An early Notice of Allowance is earnestly solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution, the undersigned can be reached at the telephone number indicated below.

Finally, if there are any fees due in connection with the filing of this paper, please charge the fees to Deposit Account No. 08-3425.

Respectfully submitted,

Date: May 3, 2002



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: **Yu, et al.**

Application Number: 09/589,285

Group Art Unit: 1646

Filed: June 8, 2000

Examiner: Prasad, S.

Title: **Methods of Treatment of Immune
System Related Disorders Using
Neutrokin-alpha (as amended)**

Atty. Docket No. PF343P3C4

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Amendments are shown in bold with insertions indicated with underlining and deletions indicated by strikeout.

In the Specification:

The current Specification has been replaced with the Substitute Specification filed herewith.

In the Sequence Listing:

The current Sequence Listing has been replaced with the Substitute Sequence Listing submitted herewith.

In the Claims:

Claims 17, 19, 26-88, 96, 97, 105, 106, 111, 112, 117, 118, 120, 122-125, 131, 132, 134, 136-139, 145, 146, 148, 150-211, 219-220, 228, 229, 234, 235, 243, 244, 257, 258, 268, and 269 have been cancelled without prejudice or disclaimer.

New Claims 275-278 have been added.

Claims 89, 98, 113, 119, 121, 126, 133, 135, 140, 142, 144, 147, 149, 212, 221, 226, 230, 233, 236, and 250 have been replaced with the following amended claims:

89. (Once Amended) A method of treating an immunodeficiency comprising administering to an individual, a therapeutically effective amount of a protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of amino acid residues n to 285 of SEQ ID NO:2, where n is an integer in the range of 2-190;

(b) the amino acid sequence of amino acid residues 1 to m of SEQ ID NO:2, where m is an integer in the range of 274 to 284; and

(c) the amino acid sequence of amino acid residues n to m of SEQ ID NO:2, where n is an integer in the range of 2-190 and m is an integer in the range of 274-284;

wherein the polypeptide having said amino acid sequence modulates lymphocyte proliferation, differentiation, or survival.

98. (Once Amended) A method of treating an immunodeficiency comprising administering to an individual, a therapeutically effective amount of a protein comprising a first amino acid sequence that is 95% or more identical to a second amino acid sequence selected from the group consisting of:

(a) ~~(d)~~ the amino acid sequence of amino acid residues n to 285 of SEQ ID NO:2, where n is an integer in the range of 2-190;

(b) ~~(e)~~ the amino acid sequence of amino acid residues 1 to m of SEQ ID NO:2, where m is an integer in the range of 274 to 284; and

(c) ~~(f)~~ the amino acid sequence of amino acid residues n to m of SEQ ID NO:2, where n is an integer in the range of 2-190 and m is an integer in the range of 274-284;

wherein the polypeptide having said first amino acid sequence modulates lymphocyte proliferation, differentiation, or survival.

113. (Once Amended) A method of treating an ~~immune system disease or disorder~~ immunodeficiency comprising administering to an individual, a therapeutically effective amount of a protein comprising the amino acid sequence of amino acid residues 134-285 of SEQ ID NO:2.

119. (Once Amended) The method of claim 113 wherein the ~~immune system disease or disorder~~ immunodeficiency is ~~an autoimmune system disease or disorder~~ common variable immunodeficiency (CVID).

121. (Once Amended) The method of claim 113 wherein the ~~immune system disease or disorder~~ immunodeficiency is ~~an immunodeficiency~~ Selective IgA deficiency.

126. (Once Amended) A method of treating an ~~immune system disease or disorder~~ immunodeficiency comprising administering to an individual, a therapeutically effective amount of a protein consisting of a first amino acid sequence which is 90% or more identical to a second amino acid sequence consisting of amino acid residues 134-285 of SEQ ID NO:2, wherein the polypeptide having said first amino acid sequence modulates lymphocyte proliferation, differentiation, or survival.

133. (Once Amended) The method of claim 126 wherein the ~~immune system disease or disorder~~ immunodeficiency is ~~an autoimmune system disease or disorder~~ common variable immunodeficiency (CVID).

135. (Once Amended) The method of claim 126 wherein the ~~immune system disease or disorder~~ immunodeficiency is ~~an immunodeficiency~~ Selective IgA deficiency.

140. (Once Amended) A method of treating an ~~immune system disease or disorder~~ immunodeficiency comprising administering to an individual, a therapeutically effective amount of a protein comprising a first amino acid sequence which is 90% or more identical to a second amino acid sequence consisting of amino acid residues 134-285 of SEQ ID NO:2, wherein the polypeptide having said first amino acid sequence modulates lymphocyte proliferation, differentiation, or survival.

142. (Once Amended) The method of claim ~~141~~ 140 wherein the protein also comprises a heterologous amino acid sequence.

144. (Once Amended) The method of claim ~~126-140~~ wherein said protein is labeled.

147. (Once Amended) The method of claim ~~126-140~~ wherein the ~~immune system disease or disorder~~ immunodeficiency is ~~an autoimmune system disease or disorder~~ common variable immunodeficiency (CVID).

149. (New) The method of claim ~~126-140~~ wherein the ~~immune system disease or disorder~~ immunodeficiency is ~~an immunodeficiency~~ Selective IgA deficiency.

212. (Once Amended) A method of stimulating leukocyte ~~activation or proliferation,~~ differentiation or survival comprising administering to an individual, a therapeutically effective amount of a protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of amino acid residues n to 285 of SEQ ID NO:2, where n is an integer in the range of 2-190;

(b) the amino acid sequence of amino acid residues 1 to m of SEQ ID NO:2, where m is an integer in the range of 274 ~~to~~ 284; and

(c) the amino acid sequence of amino acid residues n to m of SEQ ID NO:2, where n is an integer in the range of 2-190 and m is an integer in the range of 274-284;

wherein the polypeptide having said amino acid sequence modulates lymphocyte proliferation, differentiation, or survival.

221. (Once Amended) A method of stimulating leukocyte ~~activation or~~ proliferation, **differentiation or survival** comprising administering to an individual, a therapeutically effective amount of a protein comprising a first amino acid sequence that is 95% or more identical to a second amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of amino acid residues n to 285 of SEQ ID NO:2, where n is an integer in the range of 2-190;

(b) the amino acid sequence of amino acid residues 1 to m of SEQ ID NO:2, where m is an integer in the range of 274 ~~to~~ 284; and

(c) the amino acid sequence of amino acid residues n to m of SEQ ID NO:2, where n is an integer in the range of 2-190 and m is an integer in the range of 274-284;

wherein the polypeptide having said first amino acid sequence modulates lymphocyte proliferation, **differentiation, or survival**.

226. (Once Amended) The method of claim ~~226~~**225** wherein the heterologous amino acid sequence is the amino acid sequence of an immunoglobulin Fc domain.

230. (Once Amended) A method of stimulating leukocyte ~~activation or~~ proliferation, **differentiation or survival** comprising administering to an individual, a therapeutically effective amount of a protein consisting of an amino acid sequence of amino acid residues 134-285 of SEQ ID NO:2.

233. (Once Amended) The method of claim ~~221-230~~ wherein said protein is labeled.

236. (Once Amended) A method of enhancing host defenses against infection comprising administering to an individual, a therapeutically effective amount of a protein comprising an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of amino acid residues n to 285 of SEQ ID NO:2, where n is an integer in the range of 2-190;

(b) the amino acid sequence of amino acid residues 1 to m of SEQ ID NO:2, where m is an integer in the range of 274 ~~to~~ 284; and

(c) the amino acid sequence of amino acid residues n to m of SEQ ID NO:2, where n is an integer in the range of 2-190 and m is an integer in the range of 274-284;

wherein the polypeptide having said amino acid sequence modulates lymphocyte proliferation, **differentiation, or survival**.

250. (Once Amended) A method of enhancing host defenses against infection comprising administering to an individual, a therapeutically effective amount of a protein comprising a first amino acid sequence that is 95% or more identical to a second amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of amino acid residues n to 285 of SEQ ID NO:2, where n is an integer in the range of 2-190;

(b) the amino acid sequence of amino acid residues 1 to m of SEQ ID NO:2, where m is an integer in the range of 274 ~~to~~ 284; and

(c) the amino acid sequence of amino acid residues n to m of SEQ ID NO:2, where n is an integer in the range of 2-190 and m is an integer in the range of 274-284;

wherein the polypeptide having said first amino acid sequence modulates lymphocyte proliferation, **differentiation, or survival**.